REMARKS

The Office Action dated January 19, 2006 has been received and carefully studied.

A Request for Continued Examination is filed concurrently herewith.

The Examiner maintains the rejection of claims 1, 7-10, 13-15, 18, 19 and 21 under 35 U.S.C. §112, second paragraph, for reasons of record. By the accompanying amendment, the metabolite language has been removed from claim 1. With regard to language "substantially free of its corresponding R-isomer", submitted herewith is a Declaration from Dr. George Wright, attesting to the fact that such a term is clear, definite, and pervasive in the field.

The Examiner maintains the rejection of claims 1, 7-10, 13-15, 18-19 and 21 under 35 U.S.C. §112, first paragraph. By the accompanying amendment, claim 21 has been amended to recite that the purity is optical purity.

With regard to claims 1, 7-10, 1-15 and 18-19, it is noted that claim 1 recites a composition and no new matter has been added to this claim. Regarding claim 7, by the accompanying amendment, claim 7 has been amended to recite that the various diseases are those for which ketotifen is known to be effective. It is believed that the amendments overcome the rejection.

The Examiner maintains the rejection of claims 1, 7-10, 13, 15, 18, 19 and 21 under 35 U.S.C. §103(a) as being unpatentable

over Aberg I, WO 98/56381 or Aberg II, WO 98/43640 in view of Polivka I or Polivka II.

The rejection is respectfully traversed.

Applicants previously disagreed with the Examiner's unsupported statement that because ketotifen is known to be optically active as shown by Polivka I and II, one of ordinary skill in the art would "expect" norketotifen to be optically active. The Examiner now draws Applicants' attention to Kennedy (Research and Clin. Forum, v.4, p. 17-20), wherein it is stated that "the demethylated product has pharmacological activity similar to ketotifen" on page 17, in support of the Examiner's contention. However, this references does not support the Examiner's contention. This reference says nothing about the optical activity of ketotifen or norketotifen. The issue at hand is not the pharmacological activity of norketotifen versus ketotifen, it is first whether one skilled in the art would "expect" that just because Polivka I and II show that ketotifen has optical activity, norketotifen would exhibit optical activity, and second, even if such an expectation were present, whether one would expect that the S-isomer of norketotifen would be devoid of the severe sedative side effects of ketotifen. The Kennedy reference in no way informs this inquiry.

The Examiner next cites the Mey reference in support of her position that the atropisomerism has nothing to do with the methylation or demethylation of the piperindinyl ring. The

passage relied upon by the Examiner in the Mey reference reads as follows:

> "Ketotifen [(*R,S*)-4-(1-methyl-4-piperidylidene)-9,10-dihydro-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophene-10-one] is an oral H_1 antihistamine used in the control of asthma and other allergic conditions (Grant et al., 1990). Its cental seven-membered ring is nonplanar, giving rise to chirality, and enantiomers that differ in pharmacological potency have been separated by formation of diastereomeric salts (Polivka et al., 1989)."

It may indeed be correct that the substituted seven-membered ring structure is of importance for the chirality of ketotifen, but since not all substituted seven-membered rings form the basis for stable atropisomerism, the scientific question here is how the ketotifen atropisomers were stabilized in one of the two configurations that are called R and S. Without stabilization there are no stable atropisomers. Experienced synthetic chemists, highly skilled in the art of chiral chemistry -- such as the present inventors Drs. Wright and Chen -- were initially of the opinion that the methyl-substituent of the piperidine-nitrogen was an important and necessary stabilizing moiety for the atropisomers of ketotifen. There was no reasonable expectation that norketotifen, which is devoid of that methyl group, would exhibit similar atropisomers to ketotifen, and that they actually would be stable -- if they existed at all. Furthermore, and teaching away from the present invention,

is the fact that the atropisomers of norketotifen could not be synthesized using any known or described methodology; the present inventors were faced with the double problem of trying to make atropisomers that might not even exist.

Since the present inventors have now found that there are stable atropisomers of norketotifen, it can now be concluded that the methyl group on the piperidine is not needed for the stabilization of the current atropisomers and with the help of hindsight, this surprising finding can now be stated as a fact, as has been done by the Examiner. But the proper inquiry must not use such hindsight; it must be based upon the prior art existing at the time the invention was made. That prior art provides no reasonable expectation that norketotifen has stable optical isomers. Applicants note that it is now the opinion of the present inventors that the existence of stable optical isomers of norketotifen can be explained on the basis of the whole three-cyclic structure being forced into a non-planar configuration, thereby forming atropisomers with high energy barriers against racemization.

In any event, even if, *arguendo,* the existence of the S-isomer of norketitofen were suggested by the cited references, nowhere is there any disclosure or suggestion that the S-isomer is devoid of the severe sedative side effects of ketotifen. This alone is so surprising and unexpected that it rebuts any *prima facie* case of obviousness.

The allowance of claim 6 is noted with appreciation.

New claim 22 has been added to further define the invention.

Reconsideration and allowance are respectfully requested in view of the foregoing.

Respectfully submitted,

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